Cushing disease, which is induced by a functional ACTH-producing adenoma of the anterior pituitary gland, is the most common cause of ACTH-dependent Cushing syndrome. The treatment of Cushing disease remains challenging for neurosurgeons and endocrinologists. Transsphenoidal surgery is currently the treatment of choice in patients who harbor ACTH-secreting pituitary tumors associated with Cushing disease. This surgery provides the best option for rapid biochemical remission with excellent long-term results. Remission rates after transsphenoidal resection performed by experienced surgeons have ranged from approximately 70 to 90%. Some patients, however, will not achieve sustained remission after transsphenoidal surgery and can exhibit persistent or recurrent Cushing disease that requires multimodal treatment to achieve remission. In these patients, options for treatment include repeat transsphenoidal resection, radiation therapy (including conventional fractionated radiation therapy and stereotactic radiosurgery), and medical therapy. Despite undergoing multiple treatment modalities, some patients may ultimately require bilateral adrenalectomy for definitive treatment to eliminate hypercortisolemia associated with Cushing disease. In this article, the authors review the treatment options for patients who have persistent or recurrent Cushing disease after unsuccessful transsphenoidal surgery. The indications, current results reported in the literature, and complications of each treatment modality are discussed.

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Key Words • adrenalectomy • Cushing disease • pituitary adenoma • stereotactic radiosurgery • transsphenoidal surgery

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; GABA = γ-aminobutyric acid; GI = gastrointestinal; MR = magnetic resonance; SRS = stereotactic radiosurgery.

Repeat Transsphenoidal Surgery

As indicated earlier, transsphenoidal surgical removal of ACTH-producing pituitary adenomas is currently recommended as the first-line treatment for Cushing disease. The reported rates of remission are variable because of the wide...
variety of remission criteria from each publication. In a recent review, Utz and colleagues\textsuperscript{22} reported a possible remission rate of 70 to 90% of cases; however, if patients are followed up for many years, the overall remission rate is expected to decline. For example, Atkinson and associates\textsuperscript{23} reported an overall remission rate of 56% at 9.6 years after transsphenoidal surgery.

If biochemical evidence establishes that Cushing disease is not controlled and hypercortisolism persists or recurs, repeat transsphenoidal surgery is a reasonable option, with remission rates as high as 70%.\textsuperscript{24,25,26} The timing between the first and second surgery is variable and can range from several days in the immediate postoperative period to 6 to 12 weeks. If obvious hypercortisolism persists (\( \geq 6 \mu\text{g/dl} \)) on endocrine testing at postoperative Day 3, a repeat transsphenoidal surgery should be considered in the immediate postoperative period, particularly if a pituitary tumor was detected initially on preoperative MR imaging, if a tumor was found intraoperatively, and if an ACTH-positive staining tumor was detected on histopathological analysis. If no adenoma is detected or findings on preoperative MR imaging are equivocal (which is not infrequent), a positive inferior petrosal sinus sampling study, which has a sensitivity and specificity approaching 100% for Cushing disease,\textsuperscript{27} provides the surgeon with additional evidence that ACTH production is from a pituitary source when considering reexploration.\textsuperscript{28} This strategy of early repeat transsphenoidal surgery offers a chance to achieve rapid remission of hypercortisolism before the formation of scar tissue, enabling the surgeon to recall anatomical details from the earlier operation.\textsuperscript{29}

Few investigators address the results of repeat transsphenoidal surgery in the immediate postoperative period.\textsuperscript{27,28} Ram and coworkers\textsuperscript{22} reported 17 patients who underwent repeat transsphenoidal surgery within 7 to 46 days after the initial resection. Twelve (71%) of the 17 patients attained remission after the second surgery; however, only 9 (53%) sustained remission at 84 months. During the second operation, adenomectomy with or without partial hypophysectomy was performed if a tumor was found; hemihypophysectomy was performed if a tumor was absent at the second surgery but was present either intraoperatively or histologically in the specimen from the first operation; and complete hypophysectomy was performed if a tumor was absent at both surgeries.

Friedman et al.\textsuperscript{29} also reported a similar remission rate of 73% in 33 patients who underwent an unsuccessful initial transsphenoidal surgery; however, hypercortisolism recurred in 13% at 10 to 47 months postoperatively. A recent study included 44 patients with Cushing disease who underwent second transsphenoidal surgery.\textsuperscript{30} Initial remission in this study was attained in 57% with further relapse in 25%. Locatelli and associates\textsuperscript{31} used more stringent criteria for a biochemical cure and defined surgical failure as a serum cortisol level that did not fall below 2 \( \mu\text{g/dl} \) at 72 hours after surgery. Twelve patients underwent immediate reoperation for persistent Cushing disease based on these criteria, and remission was achieved in 8 patients (67%). All 12 patients underwent hypophysectomy (10 total hypophysectomies, 2 subtotal hypophysectomies) rather than selective adenomectomy, and all patients had some degree of hypopituitarism, with the majority (67%) having panhypopituitarism.

No clear predictors of remission have been described in the published literature for the second transsphenoidal surgery. Some authors have reported that the presence of an adenoma on initial MR imaging or during the initial surgery is a positive predictor, whereas the absence of an adenoma during the second surgery is a negative predictor. In the report by Ram and colleagues,\textsuperscript{22} surgical or histological confirmation of an ACTH-positive adenoma that was incompletely resected during the initial operation was the most significant predictor of a successful second operation in terms of remission and avoiding hypopituitarism. Friedman et al.\textsuperscript{27} recommended repeat transsphenoidal exploration of the pituitary gland with treatment limited to selective adenomectomy. If an adenoma is identified during surgery, the chance of remission of Cushing disease is high and the risk of hypopituitarism is low; however, if no adenoma can be found and partial or complete hypophysectomy is performed, remission of hypercortisolism is less likely and the risk of hypopituitarism is greater than 50%.

Repeat transsphenoidal surgery is a relatively safe and effective treatment option with few postoperative complications. The risk of hypopituitarism is higher after repeat transsphenoidal surgery (ranging from 41 to 50%) than after the first surgery, but is still lower than that associated with radiation therapy.\textsuperscript{27,28} The degree of hypopituitarism is somewhat related to the degree of resection (partial or total hypophysectomy) attempted at the second surgery. The most frequent pituitary deficiency in surgically induced remission of Cushing disease after gonadotrophic deficiencies is growth hormone deficiency, which occurs in 13 to 65% of cases.\textsuperscript{32} Pituitary macroadenomas that secrete ACTH are rare (4–10% of all ACTH pituitary tumors);\textsuperscript{33} thus, the published data concerning remission are scarce. As expected, the remission rate of patients with these macroadenomas is dismal; in one study, it was reported to be just 30%, with further cortisol normalization/cure in about half the patients after combined second surgery, radiation therapy, and medical treatment.\textsuperscript{34}

If a patient has a recurrent or residual tumor in the sellar region with extension into the cavernous sinus, one strategy is to remove the sellar portion at the second surgery and follow that procedure with planned radiosurgery to the cavernous sinus. This option can decrease tumor volume for subsequent radiosurgery. Because of the risk of hypopituitarism from radiation exposure to the normal pituitary gland, pituitary transposition (hypophysectomy) can be performed at surgery in cases of planned radiosurgical treatment of residual pituitary adenoma within the cavernous sinus to reduce the radiation dose to the normal pituitary gland.\textsuperscript{35} During the sellar exploration for tumor resection, the pituitary gland is transposed away from the region of the cavernous sinus, and a fat and fascia graft is interposed between the normal pituitary gland and the residual tumor in the cavernous sinus. This graft increases the distance between the normal pituitary gland and the residual cavernous sinus tumor, which may reduce radiation exposure to the normal pituitary gland.

**Radiation Therapy**

Pituitary irradiation has been used for several decades as an adjunctive therapy in treating pituitary tumors, particularly for residual or recurrent tumors after resection. The
goals of this radiation therapy are to control pituitary hypersecretion associated with minimal hypopituitarism, prevent future tumor growth, and possibly diminish tumor size. Radiation therapy may serve as a primary treatment in some patients who cannot medically tolerate resection or who have tumors in a surgically inaccessible location, such as the cavernous sinus. Conventional fractionated radiation therapy has historically been the primary radiation treatment in Cushing disease, but in the last decade or so, SRS has emerged as the primary modality for radiation therapy for pituitary tumors. There is a delay from the time radiation therapy is initiated until the time it takes effect on hypercortisolemia; therefore, medical therapy is initiated and continued for some time until the radiation therapy takes effect during the lag period.

The remission rates after conventional fractionated radiation therapy have been reported to range from 56 to 84% in patients with Cushing disease. Minniti and colleagues treated 40 patients with persistent or recurrent Cushing disease after transsphenoidal surgery with conventional fractionated radiation therapy (45–50 Gy in 25–28 fractions) with a median follow-up of 9 years; the 10-year survival rate in this study was 95%. The percentage of patients with normalization of plasma cortisol was 73% at 3 years, 78% at 5 years, and 84% at 10 years. The average time to remission was 2 years. Hypopituitarism was present in 62 and 76% of patients at 5 and 10 years after radiation therapy, respectively. Estrada and associates reported similar results, with a remission rate of 83% in 30 patients after a median follow-up of 42 months (range 18–114 months). The time to remission in this study ranged from 6 to 60 months after radiation therapy, with the majority of remissions occurring in the first 2 years. There were no relapses in the patients who achieved remission. Hypopituitarism was present in 57% of the patients, and no other adverse effects were seen.

Although conventional radiation therapy has demonstrated effectiveness in controlling ACTH secretion, its related complications have limited its usefulness. The incidence of hypopituitarism after fractionated radiation therapy to the pituitary varies between 50 and 100% several years after treatment. Additional complications associated with conventional radiation therapy to the sella include radiation necrosis, cerebral vasculopathy, damage to surrounding sellar and parasellar structures (including visual damage), and the development of radiation-induced neoplasms. There is often a delay of several years between treatment and effective control of tumor growth and hormone production. Failures of conventional fractionated radiotherapy have been attributed, in part, to an inability to deliver adequate doses accurately to a small tumor volume while sparing the surrounding structures. These concerns have resulted in increased use of SRS for refractory Cushing disease. In a large review of 35 studies in which SRS was used to treat pituitary tumors, Sheehan et al. concluded that SRS appeared to lead to faster normalization of hormone levels than fractionated radiotherapy with apparently lower risk of hypopituitarism, visual deterioration, and radiation-induced neoplasms.

As reported by Sheehan and coworkers, the rates of remission for Cushing disease after SRS have ranged from 17 to 83% in series with more than 10 patients and a median follow-up of 2 years. The variability in reported remission rates is due in part to differing criteria for defining an endocrinological cure by different authors. At most centers, endocrinological remission is generally defined as a normal urinary free cortisol level in conjunction with resolution of clinical signs or a series of normal postoperative serum cortisol levels obtained throughout the day.

In one of the largest SRS series to date, Jagannathan and coworkers evaluated 90 patients with Cushing disease who underwent Gamma knife SRS at a mean dose of 23 Gy to the tumor margin with a mean follow-up of 45 months (range 12–132 months). All but one patient had unsuccessful prior transphenoidal surgery. One patient who had a cavernous sinus tumor underwent SRS as the primary treatment without resection. Biochemical remission (defined as normalization of 24-hour urinary free cortisol levels) was achieved in 49 patients (54%), with a mean time to remission of 13 months. Ten patients (20%) who achieved remission after SRS experienced relapse, with a mean time to recurrence of 27 months. This rate of relapse after initial remission emphasizes the importance of long-term, and perhaps lifelong, follow-up. Sixty-nine percent of patients had a decrease in tumor size, and 22% suffered a new hormone deficit. The most common newly developed deficit was hypothyroidism, followed by growth hormone deficiency. Sixty-nine percent of patients experienced ophthalmoplegia from a third, fourth, or sixth cranial nerve deficit, and of these, four had additional visual deficits. Of these five patients, two had previous conventional fractionated radiation therapy and four had previous SRS. One patient who had previous conventional radiation therapy and two SRS treatments developed blindness in both eyes. These results suggest that repeated radiation treatments increase the risk of optic neuropathy and cranial nerve deficit.

Although SRS appears to be a promising modality for adjunctive therapy, longer-term follow-up is necessary to determine the durability of initial remission as well as the true percentage of delayed complications from SRS, such as hypopituitarism, visual and cranial nerve neuropathy, and radiation-induced tumors. It is also important to keep in mind that if the tumor is in close proximity to the optic nerves, fractionated radiation therapy, rather than SRS, may offer a more suitable dose plan that is tolerated by the optic nerves.

Medical Therapy

Medical therapy for Cushing disease is rarely initiated as a first-line treatment, but rather serves an adjunctive role after an unsuccessful attempt at transsphenoidal resection while other treatment options are being considered or initiated. For example, medical therapy can serve as a bridging treatment until remission from radiosurgery takes effect. In some patients who cannot safely tolerate surgery, medical therapy can be considered. If medication is the only therapy, however, discontinuation of treatment will invariably result in recurrence unless another form of treatment, such as radiosurgery, is administered. Most studies regarding medical therapy for treatment of hypercortisolism were performed in patients with adrenocortical carcinoma and bilateral adrenal hyperplasia, but some reports note the use of these therapies in Cushing disease. Overall, medical treatment may be useful in up to one third of patients.

There are three potential mechanisms of action for med-
ical therapy: 1) inhibition of steroidogenesis; 2) modulation of ACTH release; and 3) receptor blockade with glucocorticoid antagonists (Table 1).

Inhibition of Steroidogenesis

Inhibitors of steroidogenesis decrease cortisol production by direct inhibition at one or more enzymatic steps, which can result in partial or complete inhibition of cortisol synthesis. The most commonly used agents of this inhibitor class are ketoconazole, mitotane, trilostane, aminoglutethimide, and metyrapone. The effectiveness of each drug as a sole therapy is controversial. Combinations of these drugs may have additive or synergistic effects, allowing smaller doses of each drug with fewer side effects. One disadvantage of the use of these agents is the need to increase the dose to maintain normal cortisol levels because the setpoint for cortisol negative feedback is higher in ACTH-secreting pituitary tumors than in the normal pituitary gland. Because the risk of adrenal insufficiency is high, frequent monitoring of plasma or urine cortisol is necessary. Another widely used approach is total blockade of the adrenal gland with glucocorticoid replacement, but the balance between normal cortisol levels and exogenous hypercortisolism is hard to maintain.

Ketoconazole is an imidazole derivative that inhibits cytochrome P450 enzymes including 17,20-lyase, 11β-hydroxylase, and 17α-hydroxylase and side-chain cleavage. The typical dosage of ketoconazole ranges from 400 to 1200 mg per day. Ketoconazole has been shown to decrease urinary cortisol levels effectively in patients with Cushing disease. A metaanalysis of 82 patients with presumed Cushing disease showed that monotherapy with ketoconazole effectively reduced plasma cortisol levels in 70%, Some reports have shown that ketoconazole prevents the expected compensatory increase in ACTH secretion in patients with Cushing disease, suggesting that it may impair ACTH release. Other investigators have shown that basal ACTH levels were increased after treatment, suggesting that the drug may not suppress corticotrope tumors. In general, the major effect of ketoconazole is on the adrenal cortex. Side effects from this drug include GI distress and gynecomastia, occurring in fewer than 15% of patients. Elevated levels of hepatic transaminases are also common, thus requiring periodic monitoring of liver function tests. Because of its favorable adverse effect profile, twice-daily dosing, and relative effectiveness as a single-agent therapy, ketoconazole has emerged as the agent of choice for the medical treatment of Cushing disease.

Metyrapone, an inhibitor of 11β-hydroxylase, may be used as monotherapy or in combination with radiation therapy for Cushing disease. In one study of 53 patients with Cushing disease, normalized urine cortisol levels were achieved in 75%, using an average dose of 2250 mg of metyrapone per day (range 750–6000 mg) over a short-term course (1–16 weeks). Metyrapone was administered long term (median 27 months, range 3–140 months) in 24 patients who had been treated with pituitary irradiation, with adequate control of hypercortisolism achieved in 20 patients (83%). Adverse effects include hypertension, acne, hirsutism, hypokalemia, edema, nausea, and dizziness.

Trilostane, a 3β-hydroxysteroid-dehydrogenase inhibitor, is a relatively weak inhibitor of steroidogenesis. It is not potent enough to block cortisol biosynthesis in patients with hypercortisolism, and thus the remission rates of patients receiving trilostane have been poor and somewhat variable. Side effects include GI discomfort, diarrhea, and paresthesias.

Aminoglutethimide inhibits the side-chain cleavage of cortisol biosynthesis (cholesterol to pregnenolone). As a monotherapy, aminoglutethimide is not very useful; instead, it is most effective when given in combination with other drugs, such as metyrapone. The dose is usually 250 mg administered two to three times daily. Side effects include GI symptoms, headache, dizziness, depression, and blurred vision.

Etomidate is an imidazole derivative that inhibits cholesterol side-chain cleavage and 11β-hydroxylase. It has a strong inhibitory effect and has been shown to reduce plasma cortisol levels in patients with Cushing disease. Etomidate is the only agent that can be given to patients intravenously.

**TABLE 1**

<table>
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<tr>
<th>Medical therapy for Cushing disease</th>
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<tr>
<td><strong>drugs that inhibit steroidogenesis</strong></td>
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<td><strong>drugs that modulate ACTH release</strong></td>
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<td><strong>cortisol-receptor antagonists</strong></td>
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<td>mifepristone (RU-486)</td>
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Modulation of ACTH Release

Because ACTH hypersecretion remains under hypothalamic and pituitary control in Cushing disease, neuromodulatory agents, such as neurotransmitter agonists and antagonists acting on the hypothalamic-pituitary axis, can influence ACTH or CRH release. Neuromodulatory agents have been used in patients with Cushing disease after unsuccessful transsphenoidal surgery or radiation therapy with mixed results. No randomized trials have been described, and most of the positive results are due to acute administration, leaving the real therapeutic potential unknown.

The most frequently used ACTH release modulators are somatostatin analogs (octreotide), dopamine agonists (bromocriptine), serotonin antagonists (cyproheptadine, ritanserin), and GABA agonists (sodium valproate). Their efficacy is variable between patients, and the exact mechanism of lowering ACTH is not completely understood. None of these agents has demonstrated consistent clinical efficacy.

Octreotide, a somatostatin analog, is generally ineffective in lowering ACTH levels in Cushing disease. Octreotide was shown to inhibit CRH-stimulated ACTH secretion in vitro but not in vivo. This discrepancy was thought to be related to downregulation of somatostatin receptors by circulating cortisol in the presence of hypercortisolism. On the other hand, octreotide suppresses ACTH release in patients with Nelson syndrome. Combined treatment with octreotide and ketoconazole appeared to have an additive effect in normalizing urinary cortisol levels in three of four patients with severe ACTH-dependent hypercortisolism.

More recently, a novel multiligand somatostatin analog, SOM230, has been demonstrated to inhibit ACTH release in human corticotrope cells in vitro by interacting with somatostatin receptor Type 5. Preliminary in vivo results suggest that SOM230 could be a promising drug in medical therapy for patients with Cushing disease; however, a longer follow-up is necessary to evaluate its therapeutic efficacy.

Bromocriptine is a potent dopamine receptor agonist. The exact mechanism of action on ACTH modulation is not known; however, some investigators have suggested dopaminergic modulation of ACTH via CRH release, as well as direct suppression of ACTH. Approximately 40% of patients had normalized urine or plasma cortisol levels after chronic bromocriptine treatment. Unfortunately, the ACTH response to a single dose of bromocriptine does not predict which patients respond to long-term therapy, and thus, higher doses may be needed to achieve a response. Bromocriptine reduced plasma ACTH levels in 12 patients postadrenalectomy with elevated ACTH levels in the absence of a pituitary macroadenoma. Yet there was no significant change when bromocriptine was combined with cyproheptadine. Long-term treatment with cabergoline (0.5 mg twice a week) resulted in a complete remission of Nelson syndrome, including normalization of ACTH levels and resolution of a pituitary macroadenoma.

Cyproheptadine, a serotonin antagonist, was reported to normalize plasma ACTH and cortisol levels in patients with Cushing disease with a remission rate ranging from 30 to 50%. Hypercortisolism recurred in some patients, however, despite continued use. The use of cyproheptadine has not been consistently favorable; side effects include somnolence and hyperphagia resulting in weight gain.

Sodium valproate increases endogenous GABA by inhibiting GABA-aminotransferase. This inhibition potentiates the effect of GABA and may inhibit CRH and hence ACTH release. Results have been variable in studies of the administration of sodium valproate to decrease ACTH levels in patients with Cushing disease. In the most recent study of 19 patients, sodium valproate was not useful either as alternative or adjunctive therapy to surgery.

Cortisol Receptor Antagonists

Mifepristone (RU-486) is a steroid that binds competitively to glucocorticoid, androgen, and progestin receptors and inhibits the action of the endogenous ligands. Its has been mostly used in ectopic Cushing syndrome. Mifepristone suppresses the peripheral features of chronic hypercortisolism in nonpituitary-dependent Cushing syndromes. In Cushing disease, administration of mifepristone immediately induces a strong and long-lasting elevation of cortisol, reflecting corticotrope disinhibition. In one case, mifepristone was used in a patient with Cushing disease who underwent an unsuccessful combination of surgery, radiation treatment, and medical therapy. The treatment (up to 25 mg/kg/day of mifepristone) was very effective over an 18-month period, with normalisation of all biochemical glucocorticoid-sensitive measurements. The patient developed severe hypokalemia believed to be related to excessive cortisol activation of the mineralocorticoid receptor, which responded to treatment with spironolactone.

Bilateral Adrenalectomy

Bilateral adrenalectomy is a safe, effective, and definitive treatment for patients with refractory Cushing disease who have undergone multiple treatments unsuccessfully or when immediate reversal of hypercortisolism is needed. Recently, this operation has been performed via a minimally invasive laparoscopic approach rather than by a traditional open approach because the minimally invasive approach results in fewer complications and a shorter inpatient stay. A recent series of 12 patients with Cushing disease who had not attained remission using previous treatments (such as transsphenoidal surgery, radiotherapy, and medical therapy) showed that laparoscopic adrenalectomy was successful in resolving several signs and symptoms such as proximal myopathy, hirsutism, emotional lability, and weight loss. There was also an improvement in glucose tolerance and blood pressure control in all of these patients.

Patients undergoing bilateral adrenalectomy will require lifelong mineralocorticoid and glucocorticoid replacement, but their overall quality of life is improved when compared with their health preoperatively. One major concern after adrenalectomy is the development of Nelson syndrome in patients with ACTH-secreting pituitary adenomas. Nelson syndrome is characterized by elevated serum ACTH levels, hyperpigmentation, and progressively enlarging pituitary tumors that are often invasive and, in rare cases, may develop into pituitary carcinomas. This incidence has been reported to be between 8 and 38% in some series, with corticotroph tumor progression as high as 40% over 20 years. Kemink and colleagues found that a predictive factor for developing Nelson syndrome was...
undergoing bilateral adrenalectomy at an earlier age. The incidence of Nelson syndrome after the treatment of Cushing disease is higher in children than in adults.60 Use of prophylactic pituitary radiation therapy to reduce the risk of developing Nelson syndrome is still debatable; some investigators have shown good results, whereas others have shown no significant difference.58

Conclusions

Cushing disease remains a challenging condition to treat, particularly if the disease persists or recurs after initial transsphenoidal surgery. The surgeon should be prepared to offer secondary interventions, including repeat transsphenoidal surgery, radiation therapy, medical therapy, or bilateral adrenalectomy. Some patients may need a combination of these treatments to attain remission. Long-term follow-up of patients to monitor the relapse of cortisol elevation is necessary. These patients are best cared for by a multidisciplinary neuroendocrine team at a specialized center comprised of neurosurgeons, endocrinologists, radiation oncologists, neuroophthalmologists, otolaryngologists, and general surgeons.

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References

Management of Cushing disease


